



4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2005-D-0086] (formerly Docket No. 2005D-0223)

Guidance for Industry on Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a guidance for industry entitled “Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals.” The purpose of this guidance is to provide recommendations to industry for designing nonclinical toxicity studies to determine potential late radiation effects (radiation-induced injuries occurring after a latency period of several months to years) of therapeutic radiopharmaceuticals administered systemically. The purpose of such studies is to help minimize the risk of late-occurring irreversible radiation toxicities in clinical trials of therapeutic radiopharmaceuticals. This guidance finalizes the draft guidance of the same name issued in June 2005.

DATES: Submit either electronic or written comments on Agency guidances at any time.

ADDRESSES: Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, rm. 2201, Silver Spring, MD 20993-0002. Send one self-addressed adhesive label to assist that office in processing your requests. See the

SUPPLEMENTARY INFORMATION section for electronic access to the guidance document.

Submit electronic comments on the guidance to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

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SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled “Nonclinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceuticals.” The objective of

this guidance is to provide recommendations to industry for designing nonclinical toxicity studies to determine potential late radiation effects of therapeutic radiopharmaceutical agents. This guidance is not intended to address late radiation toxicity of radiobiologicals (e.g., radiolabeled monoclonal antibodies) or to apply to diagnostic radiopharmaceuticals whose low doses are not expected to elicit late radiation toxic effects.

This guidance focuses solely on late radiation safety concerns that are unique to therapeutic radiopharmaceuticals and provides recommendations for late radiation toxicity nonclinical study designs including issues regarding good laboratory practices, species selection, dose selection, timing of study, and study parameters.

Late radiation toxicity differs from early or acute radiation toxicity. Acute radiation toxicity (e.g., bone marrow failure, nausea, vomiting, diarrhea, and oral mucositis) occurs within days to weeks of an acute dose of radiation and is often self-limiting and reversible. In contrast, late radiation toxicity (e.g., renal failure, pulmonary fibrosis, and chord transection) occurs after a latency period of several months to years during which relatively normal organ function continues. Late radiation toxicity is usually progressive and irreversible.

Therapeutic radiopharmaceuticals are typically administered systemically to treat cancer. The radiation absorbed doses delivered by therapeutic radiopharmaceuticals may be comparable to those delivered with external beam radiotherapy (XRT). At therapeutic doses of radiation, the late radiation toxicities commonly associated with XRT (e.g., brain necrosis, paralysis, pulmonary fibrosis, liver or kidney failure, and hemorrhagic cystitis) can also be seen with therapeutic radiopharmaceuticals. With XRT, if the total dose given to an organ is less than its tolerance dose, the probability of symptomatic late radiation toxicity to that organ (exclusive of estimated risks of secondary malignancy) will be minimal. The tolerance doses of most human

organs for conventional fractionated XRT are known, and are routinely used to direct the safe administration of XRT. In FDA's experience, however, there are few clinical data from which to estimate organ tolerance doses for therapeutic radiopharmaceuticals. Furthermore, late radiation toxicity has been observed when estimates of radiation absorbed doses delivered by therapeutic radiopharmaceuticals to target organs were substantially below the published XRT organ tolerance doses.

Therefore, there is a need to gain additional knowledge in this area to support the safe administration of therapeutic radiopharmaceuticals to humans. Because studies in humans would be unethical, the best means to gain insight into this issue is by conducting nonclinical late radiation toxicity studies. These studies will aid in identifying organs at risk and establish a margin of safety for late radiation toxicity. As a result, these studies will help to minimize the risk of late-occurring radiation toxicities in clinical trials of therapeutic radiopharmaceuticals.

This guidance finalizes the draft guidance of the same name issued in June 2005 and includes edits based on public comments to improve clarity.

This guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the Agency's current thinking on nonclinical evaluation of late radiation toxicity of therapeutic radiopharmaceuticals. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) either electronic or written comments regarding this document. It is only

necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the document at either <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm> or <http://www.regulations.gov>.

Dated: November 22, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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